Supplementary Data

Treatment

The median duration of treatment was 18.4 months (range, 0.2–86.0 months) with Rd continuous, 16.6 months (range, 0.2–23.6 months) with Rd18, and 15.4 months (range, 0.02–25.3 months) with MPT. However, the median values do not take into account the long-term treatment of patients with Rd continuous, which is reflected in the mean duration of treatment (25.5, 12.6, and 11.9 months in Rd continuous, Rd18, and MPT arms, respectively). The mean number of cycles was 26.3 (range, 1–92) with Rd continuous, 13.1 (range, 1–18) with Rd18, and 8.2 (range, 1–12) with MPT.

Analysis of PFS by age

Similar to results from previous analyses, patients age 75 years or younger had a 36% reduction in the risk of progression or death with Rd continuous compared with MPT (HR, 0.64; 95% CI, 0.54–0.77) and a 34% risk reduction with Rd continuous vs Rd18 (HR, 0.66; 95% CI, 0.55-0.80). This benefit was also observed in patients older than 75 years, with a 22% reduction in the risk of progression or death with Rd continuous than with MPT (HR, 0.78; 95% CI, 0.60–0.99) and a 24% risk reduction with Rd continuous than with Rd18 (HR, 0.76; 95% CI 0.59–0.98).

Analysis of OS by age

Patients aged 75 years or younger who received Rd continuous had a median OS that was significantly longer than that in patients who received MPT (66.9 vs 55.7 months; HR, 0.78; 95% CI, 0.63–0.95) and similar to that in patients who received Rd18 (71.5 months; HR, 1.03; 95% CI, 0.83–1.28). Among patients who were older than age 75 years, those who received Rd continuous had a longer median OS than those who received MPT (48.3 months vs 37.8 months; HR, 0.78; 95% CI, 0.61-1.00) and an OS similar to that in patients who received Rd18 (45.7 months; HR, 1.00; 95% CI 0.78–1.30).

Table S1. Starting Doses

Age	Lenalidomide		Dexamethasone	
75 years or less	CrCl: less than 30 mL/min CrCl: 30-50 mL/min CrCl: more than 50 mL/min	15 mg QOD 10 mg 25 mg	40 mg	
Over 75 years	CrCl: less than 30 mL/min CrCl: 30-50 mL/min CrCl: more than 50 mL/min	15 mg QOD 10 mg 25 mg	20 mg	
Age	**Melphalan**		**Prednisone**	**Thalidomide**
75 years or less	0.25 mg/kg CrCl: less than 50 mL/min, ANC: less than 1.5×10^9/L, and platelet count: less than 100×10^9/L	0.125 mg/kg	2 mg/kg	2 mg/kg
Over 75 years	0.20 mg/kg CrCl: less than 50 mL/min, ANC: less than 1.5×10^9/L, and platelet count: less than 100×10^9/L	0.10 mg/kg	200 mg	100 mg

ANC, absolute neutrophil count; CrCl, creatinine clearance; QOD, every other day.

Table S2. Baseline Cytogenetics

	Rd Continuous (n = 248)	Rd18 (n = 261)	MPT (n = 253)	Total (n = 762)
High risk, n (%)	43 (17)	52 (20)	47 (19)	142 (19)
t(4;14)	22 (9)	23 (9)	25 (10)	70 (9)
t(14;16)	7 (3)	11 (4)	10 (4)	28 (4)
del(17p)	16 (6)	20 (8)	16 (6)	52 (7)
Standard risk, n (%)	205 (83)	209 (80)	206 (81)	620 (81)

MPT, melphalan, prednisone, and thalidomide; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

Table S3. Patient Disposition

	Rd Continuous (n = 535)	Rd18 (n = 541)	MPT (n = 547)
Still on treatment, n (%)	52 (10)	0	0
Still in follow-up phase, n (%)	20 (4)	26 (5)	24 (4)
Discontinued study, n (%)	463 (87)	515 (95)	523 (96)
Disease progression	271 (51)	362 (67)	337 (62)
Adverse event	64 (12)	71 (13)	76 (14)
Death*	60 (11)	28 (5)	37 (7)
Other	68 (13)	54 (10)	73 (13)

Numbers may not total to 100% due to rounding. * The majority of deaths after discontinuation were due to unknown reasons (Rd continuous, 9; Rd18, 4; MPT, 4) or other causes (Rd continuous, 45; Rd18, 21; MPT, 24), which most likely included adverse events on study treatment or adverse events that occurred after study discontinuation. MPT, melphalan, prednisone, and thalidomide; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

Table S4. PFS and OS by Cytogenetic Risk Groups

	Standard Risk			High Risk		
	Rd Continuous (n = 205)	Rd18 (n = 209)	MPT (n = 206)	Rd Continuous (n = 43)	Rd18 (n = 52)	MPT (n = 47)
Median PFS, mo	31.1	21.2	24.9	8.4	17.5	14.6
4-yr PFS, %	34.7	11.8	15.3	3.0	10.0	0
Median OS, mo	69.9	68.7	53.6	19.3	24.3	35.5
4-yr OS, %	65.2	61.7	57.3	33.5	30.8	29.1

MPT, melphalan, prednisone, and thalidomide; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

Table S5. Baseline Characteristics of Patients Receiving Long-Term Treatment With Rd Continuous

		Treatment With Rd Continuous		
	Baseline* (n = 535)	> 18 Months (n = 271)	≥ 3 Years (n = 138)	Ongoing† (n = 52)
Median age (range), years	73 (44-91)	72 (48-89)	71 (48-89)	70 (48-83)
Over 75 years, %	35	31	26	21
Female, n (%)	241 (45)	118 (44)	64 (46)	27 (52)
ECOG PS score, n (%)				
0	155 (29)	95 (35)	54 (39)	21 (40)
1	257 (48)	129 (47)	57 (41)	21 (40)
2	119 (22)	46 (17)	26 (19)	9 (17)
3 or higher	2 (< 1)	1 (< 1)	1 (1)	1 (2)
Data not available	2 (< 1)	0	0	0
ISS stage, n (%)				
I/II	319 (60)	180 (66)	102 (74)	39 (75)
III	216 (40)	91 (34)	36 (26)	13 (25)
Lactate dehydrogenase (U/L), n (%)				
Less than 200	448 (84)	242 (89)	125 (91)	47 (90)
200 or greater	86 (16)	28 (10)	12 (9)	5 (10)
Missing	1 (< 1)	1 (1)	0	1 (< 1)
Creatinine clearance (ml/min), n (%)				
Less than 60	267 (50)	125 (46)	60 (43)	19 (37)
Less than 30	45 (8)	10 (4)	5 (4)	1 (2)
60 or greater	268 (50)	146 (54)	78 (57)	33 (63)
Cytogenetic profile, n/n (%)‡				
High risk	43/248 (17)	13/125 (10)	1/56 (2)	0
Standard risk	205/248 (83)	112/125 (90)	55/56 (98)	19/19 (100)

* Previously published.[8] † As of data cutoff. ‡ Determined in patients with validated fluorescence in situ hybridization results. Patients with t(4;14), t(14;16), and/or del(17p) were characterized as high risk; patients without these abnormalities were characterized as standard risk. Cytogenetic profiles were not available for 287, 146, 82, and 33 patients in the baseline, > 18 months, ≥ 3 years, and ongoing groups.
ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; Rd, lenalidomide plus low-dose dexamethasone.

Table S6. Dose in Long-Term Responders to Rd Continuous

	At Randomization*	> 18 Months (n = 271)	≥ 3 Years (n = 138)	Ongoing† (n = 52)
Patients on dexamethasone, n (%)	532 (100)	242 (89)	103 (75)	32 (62)
Patients on lenalidomide at randomized dose, n (%)	532 (100)	271 (100)	138 (100)	49 (94)
25 mg	362 (68)	196 (72)	103 (75)	37 (76)
15 mg every other day‡	44 (8)	9 (3)	4 (3)	1 (2)
10 mg	126 (24)	66 (24)	31 (22)	11 (22)

* Safety population. † As of data cutoff. ‡ Three patients with severe renal dysfunction received 15 mg lenalidomide daily in cycle 1; one patient discontinued treatment after cycle 1 and the other 2 patients subsequently had their dose and/or schedule adjusted based on routine assessments of creatinine clearance. Rd, lenalidomide plus low-dose dexamethasone.

Table S7. Depth of Response in Long-Term Responders to Rd Continuous

	> 18 Months (n = 271)	≥ 3 Years (n = 138)	Ongoing* (n = 52)
ORR, n (%)	268 (99)	138 (100)	52 (100)
CR	104 (38)	67 (49)	35 (67)
VGPR	106 (39)	51 (37)	13 (25)
PR	58 (21)	20 (14)	4 (8)
SD, n (%)	3 (1)	0	0
PD, n (%)	0	0	0
NE, n (%)	0	0	0

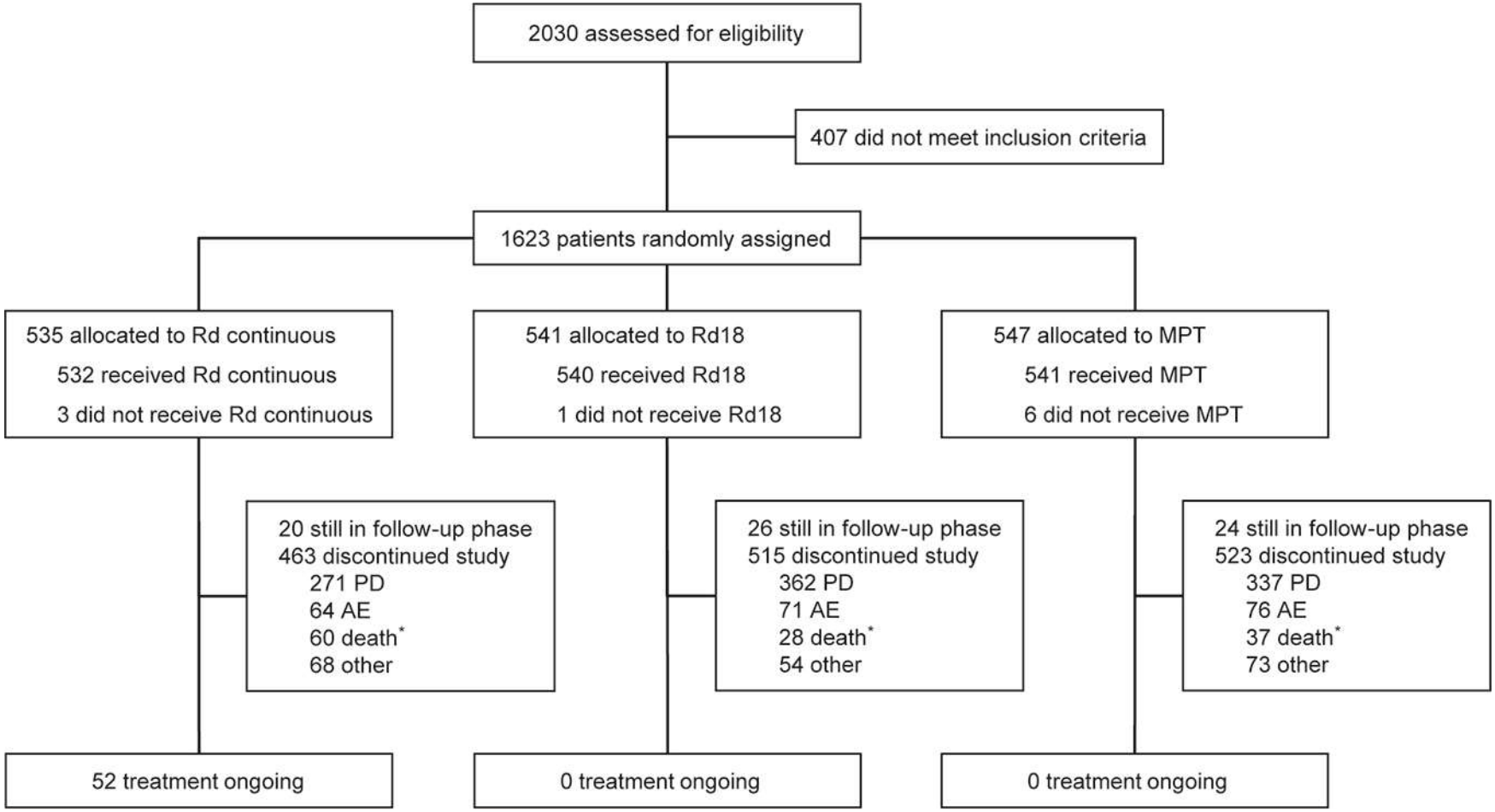
* As of data cutoff. CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; Rd, lenalidomide plus low-dose dexamethasone; SD, stable disease; VGPR, very good partial response.

Supplemental Figure legends

Figure S1. Trial Profile

The majority of deaths after discontinuation were due to unknown reasons (Rd continuous, 9; Rd18, 4; MPT, 4) or other causes (Rd continuous, 45; Rd18, 21; MPT, 24) which most likely included AEs on study treatment or AEs that occurred after study discontinuation.

AE, adverse event; MPT, melphalan, prednisone, and thalidomide; PD, progressive disease; Rd, lenalidomide plus low-dose dexamethasone; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.


2030 assessed for eligibility
407 did not meet inclusion criteria
1623 patients randomly assigned
535 allocated to Rd continuous
532 received Rd continuous
3 did not receive Rd continuous
541 allocated to Rd18
540 received Rd18
1 did not receive Rd18
547 allocated to MPT
541 received MPT
6 did not receive MPT
20 still in follow-up phase
463 discontinued study
271 PD
64 AE
60 death*
68 other
26 still in follow-up phase
515 discontinued study
362 PD
71 AE
28 death*
54 other
24 still in follow-up phase
523 discontinued study
337 PD
76 AE
37 death*
73 other
52 treatment ongoing
0 treatment ongoing
0 treatment ongoing